Exhibit 2

ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

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For the other alkyl groups, hyperconjugation is diminished because the number of C—H bonds is diminished and in *t*-butyl there are none; hence, with respect to this effect, methyl is the strongest electron donor and *t*-butyl the weakest.

However, the Baker–Nathan effect has now been shown not to be caused by hyperconjugation, but by differential solvation.[256] This was demonstrated by the finding that in certain instances where the Baker–Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.[257] Since the molecular structures are unchanged in going from the gas phase into solution, it is evident that the Baker–Nathan order in these cases is not caused by a structural feature (hyperconjugation) but by the solvent. That is, each alkyl group is solvated to a different extent.[258]

At present the evidence is against hyperconjugation in the ground states of neutral molecules.[259] However, for carbocations and free radicals[260] and for excited states of molecules,[261] there is evidence that hyperconjugation is important. In hyperconjugation in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation*,[262] the canonical forms involve not only no-bond resonance but also a charge separation not possessed by the main form. In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*:
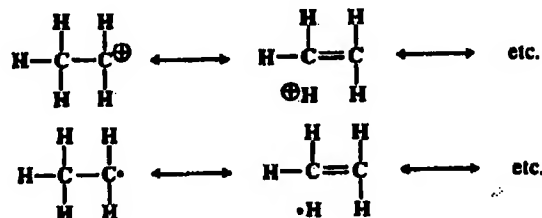
Even here the main form contributes more to the hybrid than the others.

TAUTOMERISM

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[263] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another.

[256]This idea was first suggested by Schubert; Sweeney *J. Org. Chem.* **1956**, *21*, 119.
[257]Hehre; McIver; Pople; Schleyer *J. Am. Chem. Soc.* **1974**, *96*, 7162; Arnett; Abboud *J. Am. Chem. Soc.* **1975**, *97*, 3865; Glyde; Taylor *J. Chem. Soc., Perkin Trans. 2* **1977**, 678. See also Taylor *J. Chem. Res. (S)* **1985**, 318.
[258]For an opposing view, see Cooney; Happer *Aust. J. Chem.* **1987**, *40*, 1537.
[259]For some evidence in favor, see Laube; Ha *J. Am. Chem. Soc.* **1988**, *110*, 5511.
[260]Symons *Tetrahedron* **1962**, *18*, 333.
[261]Rao; Goldman; Balasubramanian *Can. J. Chem.* **1960**, *38*, 2508.
[262]Muller; Mulliken *J. Am. Chem. Soc.* **1958**, *80*, 3489.
[263]For reviews, see Toullec *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77; Kol'tsov; Kheifets *Russ. Chem. Rev.* **1971**, *40*, 773-788, **1972**, *41*, 452-467; Forsén; Nilsson in Zabicky, Ref. 246, vol. 2, pp. 157-240.

Keto-Enol Tautomerism[264]

A very common form of tautomerism is that between a carbonyl compound containing an
α hydrogen and its enol form:[264a]
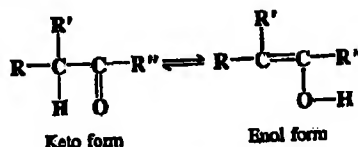
Keto form   Enol form

In simple cases (R″ = H, alkyl, OR, etc.) the equilibrium lies well to the left (Table 2.1).
The reason can be seen by examining the bond energies in Table 1.7. The keto form differs
from the enol form in possessing a C—H, a C—C, and a C=O bond where the enol has a
C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal/mol
(1500 kJ/mol) and of the second three is 347 kcal/mol (1452 kJ/mol). The keto form is
therefore thermodynamically more stable by about 12 kcal/mol (48 kJ/mol) and enol forms
cannot normally be isolated.[272a] In certain cases, however, a larger amount of the enol form

TABLE 2.1 The enol content of some carbonyl
compounds

Compound	Enol content, %	Ref.
Acetone	6×10^{-7}	265
$PhCOCH_3$	1.1×10^{-6}	266
Cyclopentanone	1×10^{-6}	267
CH_3CHO	6×10^{-5}	268
Cyclohexanone	4×10^{-5}	267
Butanal	5.5×10^{-4}	269
$(CH_3)_2CHCHO$	1.4×10^{-2}	270
Ph_2CHCHO	9.1	271
CH_3COOEt	No enol found[a]	267
CH_3COCH_2COOEt	8.4	272
$CH_3COCH_2COCH_3$	80	272
$PhCOCH_2COCH_3$	89.2	267
$EtOOCCH_2COOEt$	7.7×10^{-3}	267
$NCCH_2COOEt$	2.5×10^{-1}	267

[a]Less than 1 part in 10 million.

[264]The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction 2-3).
[264a]For a treatise, see Rappoport *The Chemistry of Enols*; Wiley: New York, 1990.
[265]Tapuhi; Jencks *J. Am. Chem. Soc.* 1982, *104*, 5758; Chiang; Kresge; Tang; Wirz *J. Am. Chem. Soc.* 1984, *106*,
460. See also Hine; Arata *Bull. Chem. Soc. Jpn.* 1976, *49*, 3089; Guthrie *Can. J. Chem.* 1979, *57*, 797, 1177; Dubois;
El-Alaoui; Toullec *J. Am. Chem. Soc.* 1981, *103*, 5393; Toullec *Tetrahedron Lett.* 1984, *25*, 4401; Chiang; Kresge;
Schepp *J. Am. Chem. Soc.* 1989, *111*, 3977.
[266]Keeffe; Kresge; Toullec *Can. J. Chem.* 1986, *64*, 1224.
[267]Gero *J. Org. Chem.* 1954, *19*, 469, 1960; Keeffe, Kresge; Schepp *J. Am. Chem. Soc.* 1990, *112*, 4862. See these
papers for values for other simple compounds.
[268]Chiang; Hojatti; Keeffe; Kresge; Schepp; Wirz *J. Am. Chem. Soc.* 1987, *109*, 4000.
[269]Bohne; MacDonald; Dunford *J. Am. Chem. Soc.* 1986, *108*, 7867.
[270]Chiang; Kresge; Walsh *J. Am. Chem. Soc.* 1986, *108*, 6314; Ref. 269.
[271]Chiang; Kresge; Krogh *J. Am. Chem. Soc.* 1988, *110*, 2600.
[272]Moriyasu; Kato; Hashimoto *J. Chem. Soc., Perkin Trans. 2* 1986, 515.
[272a]For reviews on the generation of unstable enols, see Kresge *Pure Appl. Chem.* 1991, *63*, 213-221; Capon, in
Rappoport, Ref. 264a, pp. 307-322.

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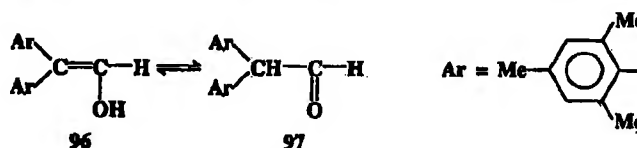[276]Biai
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is present, and it can even be the predominant form.[273] There are three main types of the more stable enols:[274]

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. As the table shows, carboxylic esters have a much smaller enolic content than ketones. In molecules like acetoacetic ester, the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:

$$CH_3-C \overset{CH}{=} C \overset{OEt}{} \\ O \cdots H-O$$
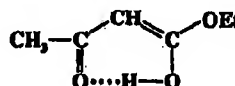
2. Molecules that contain two or three bulky aryl groups.[275] An example is 2,2-dimesitylethenol (96). In this case the keto content at equilibrium is only 5%.[276] In cases

$$\underset{Ar}{\overset{Ar}{>}}C=C \overset{H}{\underset{OH}{}} \rightleftharpoons \underset{Ar}{\overset{Ar}{>}}CH-C \overset{H}{\underset{O}{}} \qquad Ar = Me-\overset{Me}{\underset{Me}{\bigcirc}}$$

96   97

such as this steric hindrance (p. 161) destabilizes the keto form. In 96 the two aryl groups are about 120° apart, but in 97 they must move closer together (~109.5°). Such compounds are often called *Fuson-type enols.*[277]

3. Highly fluorinated enols, an example being 98.[278]

$$CF_2=C \overset{}{\underset{OH}{}} -CF_3 \xrightarrow[3h]{200°} CF_2H-C \overset{}{\underset{O}{}} -CF_3$$

98   99
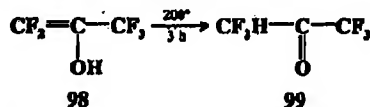
In this case the enol form is not more stable than the keto form (it is less stable, and converts to the keto form upon prolonged heating). It can however be kept at room temperature for long periods of time because the tautomerization reaction (2-3) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39°C, while the enol is a liquid even at −78°C. Each can be kept at room temperature for days if catalysts such as acids or bases are rigorously excluded.[279] Even the simplest enol, vinyl alcohol $CH_2=CHOH$, has been prepared in the

[273]For reviews of stable enols, see Kresge *Acc. Chem. Res.* 1990, 23, 43-48, *CHEMTECH*, 1986, 250-254; Hart; Rappoport; Biali, in Rappoport, Ref. 264a, pp. 481-589; Hart, *Chem. Rev.* 1979, 79, 515-528; Hart; Sasaoka *J. Chem. Educ.* 1980, 57, 685-688.
[274]For some examples of other types, see Pratt; Hopkins *J. Am. Chem. Soc.* 1987, 109, 5553; Nadler; Rappoport; Arad; Apeloig *J. Am. Chem. Soc.* 1987, 109, 7873.
[275]For a review, see Rappoport; Biali *Acc. Chem. Res.* 1988, 21, 442-449. For a discussion of their structures, see Kaftory; Nugiel; Biali; Rappoport *J. Am. Chem. Soc.* 1989, 111, 8181.
[276]Biali; Rappoport *J. Am. Chem. Soc.* 1985, 107, 1007. See also Kaftory; Biali; Rappoport *J. Am. Chem. Soc.* 1985, 107, 1701; Nugiel; Rappoport *J. Am. Chem. Soc.* 1985, 107, 3669; Nadler; Rappoport *J. Am. Chem. Soc.* 1987, 109, 2112; O'Neill; Hegarty *J. Chem. Soc., Chem. Commun.* 1987, 744; Becker; Andersson *Tetrahedron Lett.* 1987, 28, 1323.
[277]First synthesized by Fuson; see for example Fuson; Southwick; Rowland *J. Am. Chem. Soc.* 1944, 66, 1109.
[278]For a review, see Bekker; Knunyants *Sov. Sci. Rev. Sect. B* 1984, 5, 145-182.
[279]For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg *J. Am. Chem. Soc.* 1968, 90, 7008.

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gas phase at room temperature, where it has a half-life of about 30 min.[280] The enol Me_2C=CCHOH is indefinitely stable in the solid state at $-78°C$ and has a half-life of about 24 hours in the liquid state at 25°C.[281]

The extent of enolization[281a] is greatly affected by solvent,[282] concentration, and temperature. Thus, acetoacetic ester has an enol content of 0.4% in water and 19.8% in toluene.[283] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. As an example of the effect of temperature, the enol content of pentan-2,4-dione $CH_3COCH_2COCH_3$ was found to be 95, 68, and 44%, respectively, at 22, 180, and 275°C.[284]

When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since 100 and 101 differ only in
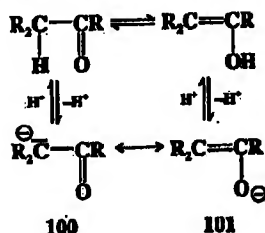

placement of electrons, *they* are not tautomers but canonical forms. The true structure of the enolate ion is a hybrid of 100 and 101 although 101 contributes more, since in this form the negative charge is on the more electronegative atom.

Other Proton-Shift Tautomerism

In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:[285]

1. Phenol-keto tautomerism.[286]

Phenol   Cyclohexadienone
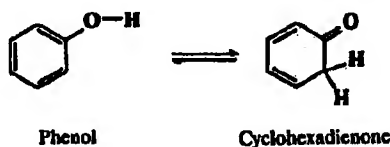
[280]Saito *Chem. Phys. Lett.* 1976, 42, 399. See also Capon; Rycroft; Watson; Zucco *J. Am. Chem. Soc.* 1981, 103, 1761; Holmes; Lossing *J. Am. Chem. Soc.* 1982, 104, 2648; McGarrity; Cretton; Pinkerton; Schwarzenbach; Flack *Angew. Chem. Int. Ed. Engl.* 1983, 22, 405 [*Angew. Chem. 95*, 426]; Rodler; Blom; Bauder *J. Am. Chem. Soc.* 1984, 106, 4029; Capon; Guo; Kwok; Siddhanta; Zucco *Acc. Chem. Res.* 1988, 21, 135-140.
[281]Chin; Lee; Park; Kim *J. Am. Chem. Soc.* 1988, 110, 8244.
[281a]For a review of keto-enol equilibrium constants, see Toullec, in Rappoport, Ref. 264a, pp. 323-398.
[282]For an extensive study, see Mills; Beak *J. Org. Chem.* 1985, 50, 1216.
[283]Meyer *Leibigs Ann. Chem.* 1911, 380, 212. See also Ref. 272.
[284]Hush; Livett; Peel; Willett *Aust. J. Chem.* 1987, 40, 599.
[285]For a review of the use of x-ray crystallography to determine tautomeric forms, see Furmanova *Russ. Chem. Rev.* 1981, 50, 775-791.
[286]For reviews, see Ershov; Nikiforov *Russ. Chem. Rev.* 1966, 35, 817-833; Forsén; Nilsson, Ref. 263, pp. 168-198.

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For most simple phenols this equilibrium lies well to the side of the phenol, since only on that side is there aromaticity. For phenol itself there is no evidence for the existence of the keto form.[287] However, the keto form becomes important and may predominate: (1) where certain groups, such as a second OH group or an N=O group, are present;[288] (2) in systems of fused aromatic rings;[289] (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[290] although in vapor phase the positions of many of these equilibria are reversed.[291] For example, in the equilibrium between 4-pyridone (102) and 4-hydroxypyridine (103), 102 is the only form detectable in ethanolic solution, while 103 predominates in the vapor phase.[291]
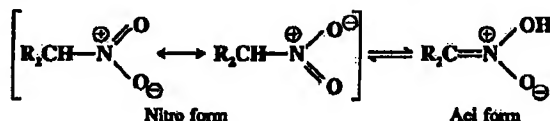

        102   103

2. Nitroso-oxime tautomerism.

$$R_2CH-N=O \rightleftharpoons R_2C=N-OH$$
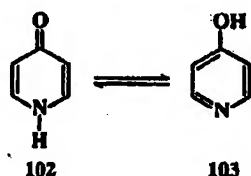
   Nitroso   Oxime
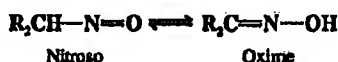
This equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is no α hydrogen.

3. Aliphatic nitro compounds are in equilibrium with aci forms.

        Nitro form   Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine-enamine tautomerism.[292]

$$R_2CH-CR=NR \rightleftharpoons R_2C=CR-NHR$$

        Imine   Enamine
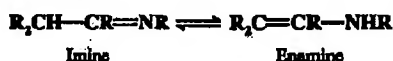
[287]Keto forms of phenol and some simple derivatives have been generated as intermediates with very short lives, but long enough for spectra to be taken at 77 K. Lasne; Ripoll; Denis *Tetrahedron Lett.* **1980**, *21*, 463. See also Capponi; Gut; Wirz *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 344 [*Angew. Chem. 98*, 358].
[288]Ershov; Nikiforov, Ref. 286. See also Highet; Chou *J. Am. Chem. Soc.* **1977**, *99*, 3538.
[289]See, for example, Majeraki; Triaajstić *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2648.
[290]For a monograph on tautomerism in heterocyclic compounds, see Elguero; Marzin; Katritzky; Linda *The Tautomerism of Heterocycles*; Academic Press: New York, 1976. For reviews, see Katritzky; Karelson; Harris *Heterocycles* **1991**, *32*, 329-369; Beak *Acc. Chem. Res.* **1977**, *10*, 186-192; Katritzky *Chimia* **1970**, *24*, 134-146.
[291]Beak; Fry; Lee; Steele *J. Am. Chem. Soc.* **1976**, *98*, 171.
[292]For reviews, see Shainyan; Mirskova *Russ. Chem. Rev.* **1979**, *48*, 107-117; Mamaev; Lapachev *Sov. Sci. Rev. Sect. B.* **1985**, *7*, 1-49. The second review also includes other closely related types of tautomerization.

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Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C=CR-NR_2$). Otherwise, the imine form predominates.[293]

Ring-chain tautomerism[294] (as in sugars) consists largely of cyclic analogs of the previous examples. There are many other highly specialized cases of proton-shift tautomerism.

Valence Tautomerism

This type of tautomerism is discussed on p. 1134.

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[293]For examples of the isolation of primary and secondary enamines, see Shin; Masaki; Ohta *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1657; de Jeso; Pommier *J. Chem. Soc., Chem. Commun.* **1977**, 565.
[294]For a monograph, see Valters; Flitsch *Ring-Chain Tautomerism*; Plenum: New York, 1985. For reviews, see Valters *Russ. Chem. Rev.* **1973**, *42*, 464–476, **1974**, *43*, 665–678; Escale; Verducci *Bull. Soc. Chim. Fr.* **1974**, 1203–1206.

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